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09/871,809	06/04/2001	Batsheva Kerem	24020X	3895

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/871,809	KEREM, BATSHEVA	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-8 are pending.

Applicants' amendment filed November 22, 2004 is acknowledged. Applicants' response has been fully considered. Claims 1, 3 and 4 have been amended, and claims 1-8 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

2. The previous rejection of claims 1-8, under 35 U.S.C. 112, second paragraph, regarding the term "a mutation" or "said abnormal expression", or identifying the gene for the mutation, is withdrawn in view of applicants' amendment to the claim and applicant' response at page 6 in the amendment filed November 22, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-8 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cell lines established from samples of cystic fibrosis (CF) patient resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising transfecting the cells with expression vector to produce a specific alternative splicing factor (ASF) such as hnRNP A1 or E4-ORF6, whereby the abnormal expression shifts towards normal expression of the gene, does not reasonably provide enablement for a method of treating individual suffering from a disease resulting from aberrant

splicing in cells due to exon inclusion, exon skipping or both exon inclusion and exon skipping, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an ASF, whereby the abnormal expression shifts towards normal expression of the gene, wherein the disease is not defined, and the ASF is not identified. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-8 are directed to a method for treating an individual suffering from a disease resulting from aberrant splicing in cells due to exon inclusion, exon skipping or both exon inclusion and exon skipping, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an ASF, whereby the abnormal expression shifts towards normal expression of the gene. The specification, however, only discloses cursory conclusions without data supporting the findings, which states that the method of invention concerns administering to the cells or to tissue or organs of the individual comprising the cells, an alternative splicing factor (ASF), e.g., any factor which is known to modulate alternative splicing, for example, members of the SR protein family including SF2/ASF, the heterogeneous ribonucleoprotein A1 (hnRNP A1), or the agonist of the naturally occurring ASFs, and the administration of the ASFs to the cells causes a shift in the expression of the gene responsible for genetic disease towards normal expression (pages 4-6). There are no indicia that the present application enables the full scope in view of a method for treating a disease resulting from aberrant splicing in cells as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858

F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the disease treated, the ASF administered, which includes various agonists of naturally occurring ASF, and the treating conditions of using ASF in various forms, e.g., as a protein product or an expression vector, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for the examples of certain cellular and viral splicing factors such as hnRNP A1 or E4-ORF6 that modulate the splicing pattern in epithelial cell line established from the sample of CF patient (Example 5, pages 14-17).

(3). The state of the prior art and relative skill of those in the art:

The related arts, e.g., Mayeda *et al.* (Mol. Cell. Biology 13, 2993-3001 (1993)) teach the essential splicing factor SF2/ASF and hnRNP A1 modulate alternative splicing *in vitro* of pre-mRNAs. An excess of SF2/ASF prevents inappropriate exon skipping in natural β-tropomyosin pre-mRNA, while an excess of hnRNP A1 does not cause inappropriate exon skipping in natural pre-mRNA; and Nordqvist *et al.* (Mol. Cell. Biology 14, 437-445 (1994)) teach the adenovirus early region 4 proteins E4 open reading frame (E4-ORF3) and E4-ORF6 regulate major late

mRNA accumulation by stimulating constitutive splicing. E4-ORF3 facilitates exon inclusion while E4-ORF6 facilitates exon skipping. However, the related art does not teach the treatment of various diseases resulting from abnormal expression of genes caused by aberrant splicing in cells, and the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on identities of the disease being treated and the ASF administered, and the treating conditions for administering ASF as a protein product or an expression vector, to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method for treating a disease resulting from aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene. As indicated in the related art (Mayeda *et al.*, Mol. Cell. Biology 13, 2993-3001 (1993)), hnRNP A1 can promote alternative exon skipping, however this effect is not universal and is dependent on the size of the internal alternative exon and on the strength of the polypyrimidine tract in the preceding of intron. The specification (e.g., Example 3, Table 2) also indicates transfection of p5T generated two splicing products: 24% of transcripts were aberrantly spliced (330 bp) and the rest (76%) were correctly spliced (513 bp), and transfection of p9T only generated 3% of transcripts being aberrantly spliced; however, transient cotransfection of p5T and pCG-A1 into COS-1 resulted in a substantial increase in aberrantly spliced transcripts (44%) and transient cotransfection of p9T and pCG-A1 does not affect the p9T minigene pattern. Thus, the invention is highly unpredictable regarding the outcome of the treatment without identifying the abnormal genes in the diseases or the ASF administered.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for treating a disease resulting from aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene. The specification indicates the effect of overexpression of the cellular hnRNP A1 on the splicing of 3849+10 kb C->T or polyT minigenes, or the effect of overexpression of the viral E4-ORF6 on the splicing of 3849+10 kb C->T minigenes (Examples 2-5; Figs.3-7), where the mutation (3849+10 kb C to T) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene has been linked to CF patients with abnormal epithelial function. However, the specification has not demonstrated the in vivo treatment of a disease, nor has indicated how to extrapolate the in vitro or ex vivo data to in vivo treatment, and there are no working examples indicating the effect of a known ASF in the treatment of the disease. Furthermore, the specification has not indicated the use of any agonist of a naturally occurring ASF, nor has demonstrated the administration of the protein product of ASF to cells is effective in shifting abnormal expression of the gene to normal expression and in the treatment of the disease. Moreover, there are no working examples indicating treating conditions such as effective amount of the ASF protein product for a specific disease in vivo. As indicated in the art (see the section of unpredictability), ASF such as hnRNP A1 can promote alternative exon skipping, however this effect is not universal. Since the specification fails to provide sufficient guidance on treating various diseases using a specific AFP, it is necessary to carry out further experimentation to assess the effects of the ASF in treating the disease resulting from aberrant splicing in cells.

(6). Nature of the Invention

The scope of the claims encompass treating a disease resulting from aberrant splicing in cells due to a mutation, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene, but the specification has not demonstrated the disease is treated with a specific AFP in vivo, and the treating conditions for various diseases using the ASF protein product. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed method, the effect of ASF and the outcome of treatment are unpredictable, and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of ASF in treating various diseases resulting aberrant splicing in cells.

In response, applicants indicate the specification demonstrated accurate "normal" splicing of affected CFTR gene products by cotransfection of COS cells with recombinant exogenous splicing factors (Example 4), and remedy of aberrant splicing of CFTR transcripts in cells of cystic fibrosis patients by expression of recombinant exogenous splicing factors (Example 5). Thus, Applicants have provided evidence of the efficacy of the claimed method in remedying the underlying genetic pathology of cystic fibrosis, a commonly used model for genetic disease of aberrant splicing; the efficacy of in-vitro models for methods of in-vivo treatment is well known in the art, as evidenced by the references presented in the response to Office Action dated September 22, 2003; and methods of treatment suitable for use with the claimed methods and pharmaceutical compositions are disclosed in the instant specification (pages 5-6). Thus, one of

ordinary skill in the art, in possession of the teachings of the present invention would be able to use the claimed methods and pharmaceutical compositions for treatment of diseases of aberrant splicing by administering ASF without undue experimentation and with a reasonable expectation of success (pages 4-6 of the response).

Applicants' response has been fully considered, however, the argument is not found persuasive because the specification does not demonstrate the use of various ASFs in the treatment of diseases resulting from aberrant splicing in cells as encompassed by the claims, and there are no working examples indicating an effective amount of a specific ASF is used in the treatment for a specific disease, Examples in specification merely demonstrate splicing pattern of CFTR transcripts carrying splicing mutations is modified by cotransfection of COS cells with recombinant exogenous splicing factors (Example 4), and the in vitro or ex vivo effect of administering a specific ASF to the cells of cystic fibrosis patients (Example 5); The post filing references provided previously do not teach the use of various ASFs (e.g., SR protein, hnRNP A1, E4-ORF3, E4-ORF6 or an undefined agonist) for the treatment of various genetic diseases, they merely indicate that it is possible to use a specific ASF such as sodium butyrate for the treatment of human SMA patient due to the results of in vitro and in vivo model. However, sodium butyrate is structurally different from other naturally occurring ASFs (see pages 7-8 of the previous Office Action), thus, the treating conditions and the effect of this compound is not applicable to other ASFs; and the specification only describes the general method of administering an ASF in the treatment of a disease (pages 5-6), and there is no disclosure regarding the use and effect of a specific ASF in the treatment of a specific disease resulting from aberrant splicing in cells. Therefore, the full scope of the claims is not enabled, and it

requires undue experimentation to assess the effect of an ASF in treating a disease resulting from aberrant splicing in cells.

4. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8 are directed to a method for treating individual suffering from a disease (e.g., cystic fibrosis) resulting from aberrant splicing in cells due to exon inclusion, exon skipping or both exon inclusion and exon skipping, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an ASF, whereby the abnormal expression shifts towards normal expression of the gene. While the specification indicates that ASF may be administered to the cells by inserting a nucleotide sequence expressing the ASF in an expression vector, and the cells of the individual are transfected with the expression vector to produce ASF, or by attaching the expression vector to targeting moiety, e.g., antibody or a ligand of a specific receptor which can specifically bind to the membranes of the desired cells, and the expression vector being administered systemically, or by administering ASF as the protein product itself (page 5, line 26-page 6, line 25), the specification does not disclose a genus of variants for ASF used in the treatment of various diseases resulting from aberrant splicing in cells.

The specification demonstrates the in vitro or ex vivo effect of administering a specific ASF to the cell lines, e.g., the effect of overexpression of the cellular hnRNP A1 on the splicing of 3849+10 kb C->T or polyT minigenes, or the effect of overexpression of the viral E4-ORF6 on the splicing of 3849+10 kb C->T minigenes (Examples 2-5; Figs.3-7), it has not demonstrated

using various ASFs in the treatment of various diseases resulting from aberrant splicing in cells, e.g., the administration of a specific ASF protein or an identified agonist of any naturally occurring ASF protein to cells in treating the disease. Furthermore, there are no in vivo working examples indicating the treating conditions such as effective amount of a specific ASF for a specific disease, and the effect of the ASF in aberrant splicing of the genes and in the treatment of disease. A description of the effect of a specific ASF on the splicing of a specific gene (Examples 2-5) does not provide original descriptive support for using ASF in the treatment of various diseases resulting from aberrant splicing in cells. The disclosure of the in vitro or ex vivo effect of administering a specific ASF to the cell lines does not meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision all the contemplated ASFs used in the treatment of various diseases resulting from aberrant splicing in cells based upon the general suggestion of method of administering an ASF in the treatment. The detailed structure of ASF (e.g., agonist of ASF) used and the treating conditions (e.g., effective amount) for various diseases must be taught, therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of preparation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a

potential method of making. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF'S were found unpatentable due to lack of written description for the broad class.

Therefore, only those embodiments described and disclosed meet the written description requirement and not the full breadth of the claim meets the written description provision of 35 USC 1 12, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1-8 are indefinite as to what effect the ASF has in the treatment of the disease since the claimed method is directed to the treatment of a disease. Claims 2-8 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

7. Claim 7 is indefinite because claim 7 does not further limit the claim (claim 6) from which it depends.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CMK
February 11, 2005